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| #1 | Search **(pla-2 or pla2) and inhibitors** | 16:57:50 | 3832 |

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Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

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MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
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1: Curr Opin Pharmacol. 2001 Apr;1(2):121-5. Related Articles, Links

# Lipoprotein-associated phospholipase A2: a potential new risk factor for coronary artery disease and a therapeutic target.

**Macphee CH**.

Department of Vascular Biology, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK. Colin_H_Macphee@sbphrd.com

The recognition that atherosclerosis represents an inflammatory disease has begun to shift interest towards novel therapies that could specifically target the underlying inflammatory component of atherogenesis. Like low-density lipoprotein, an ideal new drug target would be a modifiable plasma risk factor that not only reflects the ongoing inflammatory process but also actively promotes it. Lipoprotein-associated phospholipase A2, also known as platelet-activating factor acetylhydrolase, is a new risk factor that may have the potential to fulfil these requirements.

Publication Types:
- Review
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PMID: 11714085 [PubMed - indexed for MEDLINE]

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1: Farmaco. 2001 Jan-Feb;56(1-2):45-50. Related Articles, Links

# Lipoprotein-associated PLA2 inhibition--a novel, non-lipid lowering strategy for atherosclerosis therapy.

Leach CA, Hickey DM, Ife RJ, Macphee CH, Smith SA, Tew DG.

Glaxo SmithKline, New Frontiers Science Park, Harlow, Essex, UK. colin_leach-1@sbphrd.com

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a serine lipase that is associated with low density lipoprotein (LDL) in human plasma. Substrates include oxidised phosphatidylcholine (PC), which is hydrolysed by Lp-PLA2 to lyso-PC and oxidised fatty acids. Both products are bioactive and proinflammatory, and implicated in monocyte infiltration into the developing plaque, deposition of foam cells, and plaque progression and instability. Lp-PLA2 has recently been shown to be a risk factor for coronary events in previously asymptomatic, hypercholesterolaemic men. A series of azetidinones was designed as potent and selective inhibitors of this enzyme; SB-222657 inhibited release of the chemotactic cleavage products from oxidised LDL, and SB-244323 reduced atherosclerotic plaque development in a 3 month rabbit study. A series of pyrimidones has been designed from a screening hit, and nanomolar inhibitors identified. Oral efficacy in inhibiting plasma Lp-PLA2 in rabbits has been demonstrated with a variety of structural classes.

PMID: 11347966 [PubMed - indexed for MEDLINE]